REMARKS

Applicant respectfully requests entry of the Amendment and reconsideration of the claims. Claims 1-3 have been amended to further clarify the invention. Claims 2 and 3 are now dependent on Claim 1. Claims 4-18 have been canceled without prejudice. Claim 19 is new. After entry of the Amendment, claims 1-3 and 19 will be pending.

Support for the Amendment is found throughout the specification, including at page 8, last paragraph and Examples 1-4. Applicants submit the Amendment raises no issues of new matter.

Claim Objection

The Examiner objected to informalities in claim 1-4, 11, and 13. Claims 4, 11, and 13 have been canceled. Claims 1-3 have been amended as suggested by the Examiner. Withdrawal of the objection is respectfully requested.

35 U.S.C. 112, first paragraph

Claims 1-3 were rejected under 35 U.S.C. 112, first paragraph as lacking enablement. Applicant respectfully traverses the rejection.

The Examiner alleges the specification, while being enabling for intra-portal administration of an NO donor or agonist compound, does not enable (1) any other type of administration of an NO donor or agonist and (2) all types of compounds which fall within the scope of NO donors or agonists. Applicant does not agree.

The Examiner alleges the specification does not provide guidance for the claimed methods. Citing page 30 at lines 10-16, the Examiner alleges the disclosure admits that only intra-portal administration of the NO donor or agonist actually reverses insulin resistance. Applicant strongly disagrees.

Applicant teaches that the NO donor or agonist can be administered orally, intravenously, intramuscular, subcutaneously, or through a pump system directly into the portal vein. See, for example, the specification at page 10, lines 14-17, at page 11, lines 23-27, and at page 12, lines 9-12. The fact that intra-portal administration is exemplified as an effective mode of administration does not mean that other modes of administration are excluded. Applicant is not

required to exemplify each mode of administration to satisfy the enablement requirement. Not everything necessary to practice the invention need be disclosed. What is well known is best omitted. *In re Buckner*, 929 F.2d 660, 661 (Fed. Cir. 1991); MPEP § 2164.08. The modes of administration disclosed in the application, such as for example oral, intravenous, intramuscular, and subcutaneous administration, are well known.

Page 30 at lines 10-16 states that insulin resistance is not reversed by administration of a nitric oxide donor intravenously, but is fully reversed by administration of the same dose of nitric oxide donor directly to the liver via the portal vein. This statement does not teach or suggest that only delivery of a nitric oxide donor to the liver via the portal vein reverses insulin resistance. Reversal of insulin resistance is dependent on the concentration of nitric oxide donor in the liver. One skilled in the art would recognize that systemic administration of the nitric oxide donor would require administering a greater amount of donor to reverse insulin resistance as compared to the amount of donor that reverses insulin resistance when administered directly to the liver via the portal vein.

The Examiner alleges the specification does not enable any compound that falls within the scope of NO donors or agonists. The claims have been directed by amendment to NO donors. NO donor compounds are compounds capable of releasing nitric oxide from a more complex molecule. The specification teaches that insulin sensitivity is increased in the liver by administering a compound that stimulates NO production in the liver and shows that insulin resistance is reversed by administering an NO donor directly to the liver. The specification does not limit the NO donor to any type of NO donor compound or any specific NO donor compound. NO donor compounds are well known in the art. The function of NO donors is predictable and the level of skill in the art is high. At the time of the priority date of the present application, many types of NO donors, including synthetic NO donors, had been developed and were known to be medically useful (see for example the review by Bauer et al., 1998, *Med. Hypothesis*, 51:65-7, abstract enclosed). In view of the teachings of the specification and level of skill in the art, a skilled artisan would reasonably expect any compound that is a NO donor to be useful in the claimed methods.

In view of the forgoing, one of skill in the art would have been able to practice the claimed methods without undue experimentation. Accordingly, withdrawal of the enablement rejection is respectfully requested.

35 U.S.C. 112, second paragraph

Claims 1-3 were rejected under 35 U.S.C. § 112, second paragraph, as indefinite. Applicant respectfully traverses the rejection.

The Examiner alleges the terms "nitric oxide donor" and "nitric oxide agonist" are indefinite. The term "nitric oxide agonist" has been removed from the claims. With respect to the term "nitric oxide donor," Applicant clearly defines a nitric oxide donor as a compound that generates nitric oxide, and provides specific examples of nitric oxide donors. See, for example, the specification at:

> Page 8, lines 3-7
>
> Generally, the present invention provides a compound and method of increasing insulin sensitivity by administering an effective amount of a compound which stimulates nitric oxide production in the liver. More specifically, the compound can be administered as a nitric oxide donor or as a stimulus that generates nitric oxide within the liver.
>
> Page 8, lines 11-15
>
> The compounds of the present invention can be considered, generally, as members of the groups of nitric oxide agonists and NO donors. Examples of such compounds include, but are not limited to: 3morpholinosyndnonimine (SIN-1), sodium nitrite, nitroprusside, S-nitroso-Nacetyl-D, L-penicillamine (SNAP).

In addition, the term "nitric oxide donor" was a well-known term and many nitric oxide donors were known (see for example the review by Bauer et al., 1998, *Med. Hypothesis*, 51:65-7, abstract enclosed). Therefore, based on Applicant's disclosure and the level of skill in the art, one of skill art would reasonably understand the scope of the term nitric oxide donor.

In view of the forgoing, Applicant respectfully requests withdrawal of the indefiniteness rejection.

35 U.S.C. 102(b)

Claims 1, 2, and 9 were rejected under 35 U.S.C. § 102(b) as anticipated by Cameron et al. Applicant respectfully traverses the rejection.

The Examiner alleges an increase in insulin sensitivity would be an inherent characteristic of the treatment disclosed by Cameron et al. Applicant does not agree.

To establish inherency, the Examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teaching of the prior art. *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990). The prior inherent characteristic must be established as a certainty, probabilities are not sufficient. *In re Oelrich*, 666 F.2d 578, 581 (CCPA 1981). Cameron et al. does not disclose any treatment relating to diabetes itself, such as for example insulin resistance. Insulin resistance occurs in the prediabetic and diabetic states, which are completely different from a condition occurring in the post diabetic state as a consequence of diabetes. Cameron et al. only discloses administering a nitric oxide donor to treat a disorder (impaired microcirculation) that occurs in the post diabetic state. Cameron et al. does not teach or suggest that administering a nitric oxide donor would necessarily or for certain treat a prediabetic or diabetic state or increase insulin sensitivity. Therefore, the claimed methods do not necessarily flow from the teachings of Cameron et al.

To anticipate a claim, each and every element of the claim must be described, either expressly or inherently, in a single prior art reference. Verdegaal Bros. v. Union Oil of California, 814 F.2d 628, 631 (Fed. Cir. 1987). The reference cited by the Examiner does not teach every element of Applicant's claim. Cameron et al. does not teach administering a nitric oxide donor compound for treating insulin resistance. As discussed above, insulin resistance occurs in the prediabetic and diabetic states. In contrast, Cameron et al. only teaches administering a nitric oxide donor to treat a disorder (impaired microcirculation) that occurs in the post diabetic state. Cameron et al does not teach administering a nitric oxide donor to treat a prediabetic or diabetic state or increase insulin sensitivity. Therefore, Cameron et al. does not anticipate Applicant's claims.

Based on the foregoing, Applicants respectfully request withdrawal of the rejection under § 102(b).

Conclusion

In view of the Amendment and Remarks, Applicant respectfully requests a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

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